Scientific Research Publishing

Yangtze Medicine, 2022, 6, 41-55
https://www.scirp.org/journal/ym
ISSN Online: 2475-7349
ISSN Print: 2475-7330

Meta-Analysis of Aspirin for Primary Prevention of Stroke

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How to cite this paper: Zheng, P.P., Mao, Y.J., Yan, X.X., Ding, J.R. and Ou, Y.S. (2022) Meta-Analysis of Aspirin for Primary Prevention of Stroke. *Yangtze Medicine*, **6**, 41-55.
https://doi.org/10.4236/ym.2022.62004

Received: May 20, 2022
Accepted: June 21, 2022
Published: June 24, 2022

Abstract

Objective: This paper aims to evaluate the safety and efficacy of aspirin in primary stroke prevention by meta-analysis. **Methods**: By searching PubMed, Cochrane Library, Embase, MEDLINE, Web of Science, CNKI, China Biomedical Literature Database, VIP Database and Wanfang Database, we collected randomized controlled trials on aspirin for primary prevention of stroke. The retrieval time limit is from the establishment of the database to December 2021. Two researchers independently conducted literature search, screening, data extraction and quality evaluation, and Meta-analysis was performed using RevMan 5.3. **Results**: A total of 19 articles were included, including 220,636 subjects. Meta-analysis results show that long-term preventive use of aspirin can reduce the incidence of stroke [RR = 0.91, 95% CI (0.85, 0.98), P = 0.009], and reduce the incidence of ischemic stroke [RR = 0.84, 95% CI] (0.77, 0.91), $P < 0.0001$], reduce the incidence of TIA [RR = 0.80, 95% CI (0.72, 0.88), $P < 0.0001$], reduce the incidence of myocardial infarction [RR = 0.85, 95% CI (0.75, 0.97), $P < 0.01$], but increased the incidence of hemorrhagic stroke [RR = 1.23, 95% CI (1.04, 1.46), P = 0.01] and gastrointestinal bleeding [RR = 1.62, 95% CI (1.35, 1.93), $P < 0.01$], no significant effect on mortality [RR = 0.97, 95% CI (0.93, 1.02), P = 0.20]. **Conclusion**: Long-term prophylactic use of aspirin can reduce the overall incidence of stroke, but there is also a risk of bleeding. The advantages and disadvantages of aspirin should be fully evaluated and strict screening should be carried out before medication, which can minimize adverse reactions and improve the safety and effectiveness of aspirin in the primary prevention of stroke.

Keywords

Aspirin, Stroke, Primary Prevention, Meta-Analysis

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1. Introduction

Stroke is a cerebrovascular disease that seriously threatens the health of middle-aged and elderly people, with high morbidity, disability, mortality and recurrence rates. According to reports, the incidence of stroke in my country increases by 8.7% every year, and the mortality rate is 4 to 5 times than that of developed countries in Europe and America [1] [2]. As an anticoagulant widely used in clinic, aspirin plays an important role in the primary prevention of cardiovascular and cerebrovascular diseases. At present, although a considerable number of patients choose to take aspirin preventively every day, its primary prevention effect on cerebrovascular disease is still controversial [3]. The most controversial of these is the risk of bleeding, which has been one of the main reasons limiting aspirin's widespread clinical use. In recent years, with the continuous development of evidence-based medicine, people began to review the role of aspirin in disease prevention, but more focused on to aspirin in primary prevention of cardiovascular disease and cancer related meta-analysis [4] [5] [6], and safety and effectiveness in cerebrovascular disease primary prevention applications are rarely reported. This study searched the latest literature at home and abroad, included three large-scale clinical trials in 2018, and combined with the latest data to systematically evaluate the safety and efficacy of aspirin for primary prevention of cerebrovascular disease, in order to provide evidence-based clinical standard use of aspirin evidence.

2. Materials and Methods

2.1. Search Strategy

The randomized controlled trials of aspirin on primary prevention of stroke in PubMed, Cochrane Library, EMBASE, MEDLINE, web of science, CNKI, China biomedical literature database, VIP database and Wanfang database were searched by computer, and the included references were tracked and searched in the way of "snowball". The retrieval time limit was from the establishment of the database to December 2021. A combination of subject headings and free words were used to search, and the search terms mainly included: aspirin, acetylsalicylic acid, stroke, cerebrovascular accident, cerebrovascular disease, cardio-cerebrovascular disease, cardiovascular disease, primary prevention, randomized controlled trial. Taking PubMed as an example, its specific retrieval strategy is shown in **Figure 1**.

2.2. Inclusion Criteria

Inclusion criteria: 1) Study design. The content involves a randomized controlled trial (RCT) of aspirin in the primary prevention of stroke; 2) Research subjects. Participants were ≥18 years old; 3) Interventions included in the study. Intervention group: aspirin was routinely taken every day or every other day; control group: no or placebo at the same dose every day or every other day; 4) Outcome indicators. Primary outcome measures: stroke, ischemic stroke,

#1	aspirin
#2	acetylsalicylic acid
#3	#1 OR #2
#4	stroke
#5	cerebrovascular accident
#6	cerebrovascular disease
#7	cardio-cerebrovascular disease
#8	cardiovascular disease
#9	#4 OR#5 OR#6 OR#7 OR#8
#10	primary prevention
#11	randomized controlled trial
#12	#3 OR#9 OR#10 OR#11

Figure 1. PubMed retrieval strategy.

hemorrhagic stroke, transient ischemic attack (TIA); Secondary outcome measures: myocardial infarction, gastrointestinal bleeding, mortality.

2.3. Exclusion Criteria

Exclusion criteria: 1) Taking aspirin, having a history of gastrointestinal disease, stroke or confirmed myocardial infarction; 2) Studies for which the full text was not available or incomplete data; 3) The study type was review, case report, qualitative study; 4) No relevant outcome indicators or could not be calculated; 5) Studies published in languages other than Chinese and English.

2.4. Data Extraction

Data were extracted from all the included literatures, including: inclusion study, year, country, study type, study object, dose, follow-up years, average age, sample size, intervention measures of intervention group and control group, outcome indicators, etc.

2.5. Quality Assessment

The Cochrane Manual version 5.1.0 bias risk Assessment tool was used [7], which was completed by 3 evidence-based trained researchers, 2 of whom performed independently, and the third researcher decided in case of disagreement. The evaluation contents include: random sequence generation, allocation concealment, blinding of research subjects and implementers, blinding of outcome measurers, complete outcome data reporting, selective research reporting results, and other aspects of bias. Those who fully meet the above items indicate that various risk biases are low, and their quality grade is A; those who meet some of the items indicate that various risk biases are medium, and their quality grades are B; those who do not meet the above items at all indicate that various risk biases are high, and their quality is low. A grade of C is excluded.

2.6. Statistical Methods

Meta-analysis was performed using RevMan 5.3. The outcome indicators of this

study were all dichotomous data, so the relative risk (RR) value was calculated, and the 95% confidence interval (CI) was calculated for the effect analysis. The c^2 test was used to determine whether there was heterogeneity among the studies, and the I^2 value was used to judge the size of the heterogeneity. If $P \geq 0.1$ and $I^2 \leq 50\%$, a fixed-effect model was used for Meta-analysis; If $P < 0.1$ and $I^2 > 50\%$, the source of heterogeneity should be analyzed. If there was no obvious clinical heterogeneity, a random-effects model was used for Meta-analysis. If the heterogeneity is too large and the source cannot be judged, descriptive analysis of the results is carried out.

3. Results

3.1. Literature Search Results

A total of 3791 literatures, 887 in Chinese and 2904 in English were obtained through preliminary search, and 3 related literatures were manually searched, and a total of 3794 relevant literatures were obtained. By reading the titles and abstracts, excluding duplicate publications, reviews, and literatures inconsistent with the theme, and further reading the full text, 19 literatures were finally included, including 1 Chinese literature and 18 English literatures, including a total of 220,636 research subjects. The literature retrieval and screening process is shown in Figure 2.

3.2. Characteristics of the Included Studies

The basic characteristics of the included studies are shown in Table 1. All included literatures were strictly assessed for quality according to the Cochrane

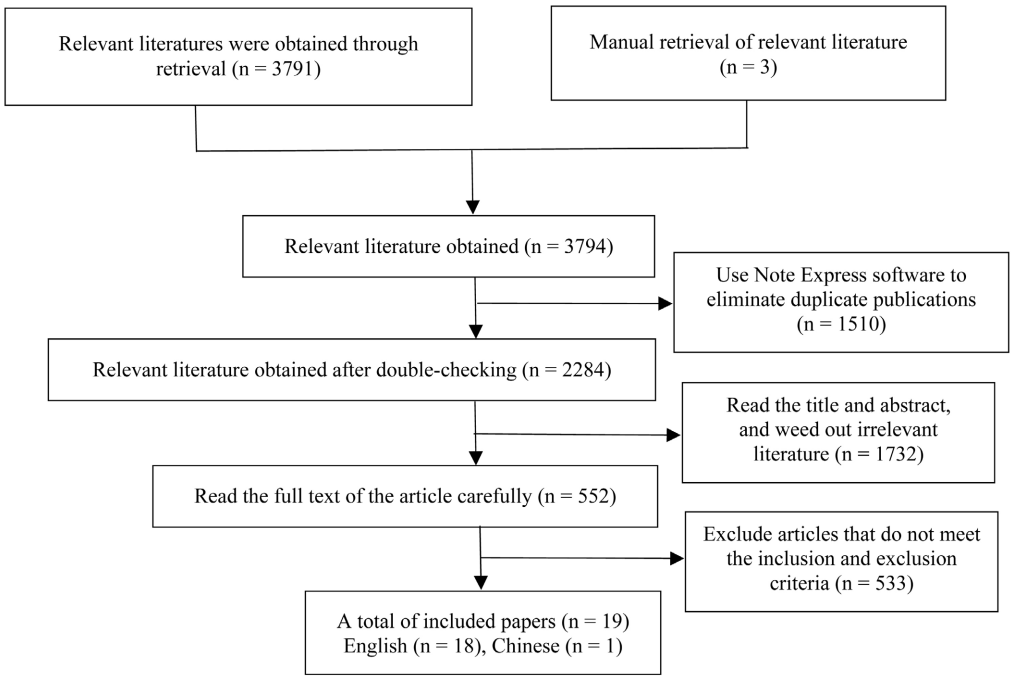

Figure 2. Literature search and screening process.

Table 1. Basic characteristics of the 19 included studies.

Included Studies	Country	Type of Study	Research Object	Dose (mg)	Tracking (year)	Average age (years)	Sample Size		Interventions		Outcome indicators	Literature quality evaluation
							Intervention	Control	Intervention	Control		
Peto *et al.* 1988 [8]	UK	RCT	Healthy male doctor	500 or 300	5.6	63.6	3429	1710	Take a daily aspirin	Not taking	①②③⑤⑦	B
PHS 1989 [9]	US	RCT	Male doctors between the ages of 40and 84	325	5	53.8	11,037	11,034	Take aspirin every other day	Take a placebo every other day	①②③⑤⑥⑦	B
Lindblad *et al.* 1993 [10]	Sweden	RCT	Patients undergoing carotid endarterectomy	75	0.5	66	117	115	Take a daily aspirin	Take a placebo daily	①④⑥	B
TPT 1998 [11]	UK	RCT	Men aged 45 to 69 years at high risk of ischemic heart disease	75	6.8	57.5	1268	1272	Take a daily aspirin	Take warfarin or a placebo daily	①②③⑤⑥⑦	A
Hansson *et al.* 1998 [12]	26 countries in North and south Europe, US, Asia	RCT	Patients aged 50 to 80 years with hypertension	75	3.8	61.5	9399	9391	Take a daily aspirin	Take a placebo daily	①②③⑥⑦	B
Meade *et al.* 2000 [13]	UK	RCT	Men between the ages of 45 and 69 with an increased risk of coronary heart disease	75	1	57.5	8105	8071	Take a daily aspirin	Take a placebo daily	①⑦	B
Roncaglioni 2001 [14]	Italian	RCT	Patients with cardiovascular risk factors	100	3.6	64.4	2226	2269	Take a daily aspirin	Not taking	①②③⑤⑥⑦	B
Sacco *et al.* 2003 [15]	Italian	RCT	Diabetic patients aged ≥ 50 years	100	3.7	64.2	519	512	Take a daily aspirin	Not taking	①④⑤⑦	B
Cleland *et al.* 2004 [16]	UK, US	RCT	Heart failure patients	300	2.3	63.5	91	89	Take a daily aspirin	Not taking	①⑤⑦	B
Ridker *et al.* 2005 [17]	US	RCT	Healthy female specialist aged ≥ 45 years	100	10.1	54.6	19,934	19,942	Take aspirin every other day	Take a placebo every other day	①②③④⑤⑥⑦	B

Continued

DPC 2006 [18]	China	RCT	Hypertensive patients aged 40 - 75 years	50 or 100	3.2	60.27	1151	1029	Take a daily aspirin	Not taking	①②③⑤⑦	B
Ogawa *et al.* 2008 [19]	Japan	RCT	Diabetic patients aged 30 - 85	81 or 100	4.37	64.5	1262	1277	Take a daily aspirin	Not taking	①②③⑤⑥⑦	B
Belch *et al.* 2008 [20]	UK	RCT	Diabetic patients aged ≥ 40 years	100	6.7	60.3	638	638	Take a daily aspirin	Take a placebo daily	①②③④⑤⑥⑦	A
Fowkes *et al.* 2010 [21]	UK	RCT	Age 50 - 75 years old and ABPI ≤ 0.95	100	8.2	62	1675	1675	Take a daily aspirin	Take a placebo daily	①②③④⑤⑥⑦	A
Kurth *et al.* 2011 [22]	US	RCT	Women aged ≥ 45 years	100	2.7	54.8	19,869	19,888	Take aspirin every other day	Take a placebo every other day	①②③④⑤⑦	B
Ikeda *et al.* 2014 [23]	Japan	RCT	Patients aged 60 to 85 with hypertension, dyslipidemia or diabetes	100	5	70.5	7220	7244	Take a daily aspirin	Not taking	①②③④⑤⑥⑦	B
McNeil *et al.* 2018 [24]	Australia, US	RCT	People aged 70 or older	100	4.7	74	9525	9589	Take a daily aspirin	Take a placebo daily	①②③⑤⑥⑦	A
Gaziano *et al.* 2018 [25]	Germany, Italy, Ireland, Poland, Spain, US and UK	RCT	Patients with cardiovascular risk factors	100	5	63.9	6270	6276	Take a daily aspirin	Take a placebo daily	①③④⑤⑥⑦	A
ASCEND *et al.* 2018 [26]	US	RCT	Patients aged ≥ 40 years with diabetes	100	7.4	63.2	7740	7740	Take a daily aspirin	Take a placebo daily	①②③④⑤⑥⑦	A

Note: ① Cerebral apoplexy; ② Ischemic stroke; ③ Hemorrhagic stroke; ④ TIA; ⑤ Myocardial infarction; ⑥ Gastrointestinal bleeding; ⑦ Mortality.

Handbook version 5.1.0 tool for assessing risk of bias [7] and their quality was graded. The results showed that of the 19 included papers [8]-[26], 6 of them [11] [20] [21] [24] [25] [26] were graded A, and 13 [8] [9] [10] [12]-[19] [22] [23] were rated B.

3.3. Outcome Indicators

3.3.1. Incidence of Stroke

19 studies [8]-[26] reported the effect of long-term prophylactic aspirin use on stroke incidence. The results showed that there was no heterogeneity among the studies (I^2 = 9%, P = 0.34). Using a fixed effect model, the incidence of stroke in

the aspirin group was lower than that in the control group [*RR* = 0.91, 95% CI (0.85, 0.98), *P* = 0.009], the difference was statistically significant, see Figure 3.

3.3.2. Incidence of Ischemic Stroke

13 studies [8] [9] [11] [14] [17]-[24] [26] reported the effect of long-term prophylactic aspirin on the incidence of ischemic stroke. The results showed that there was no heterogeneity among the studies (I^2 = 0%, *P* = 0.62). Using the fixed effect model, the incidence of ischemic stroke in the aspirin group was lower than that in the control group [*RR* = 0.84, 95% CI (0.77, 0.91), *P* < 0.0001]. The difference was statistically significant, as shown in Figure 4.

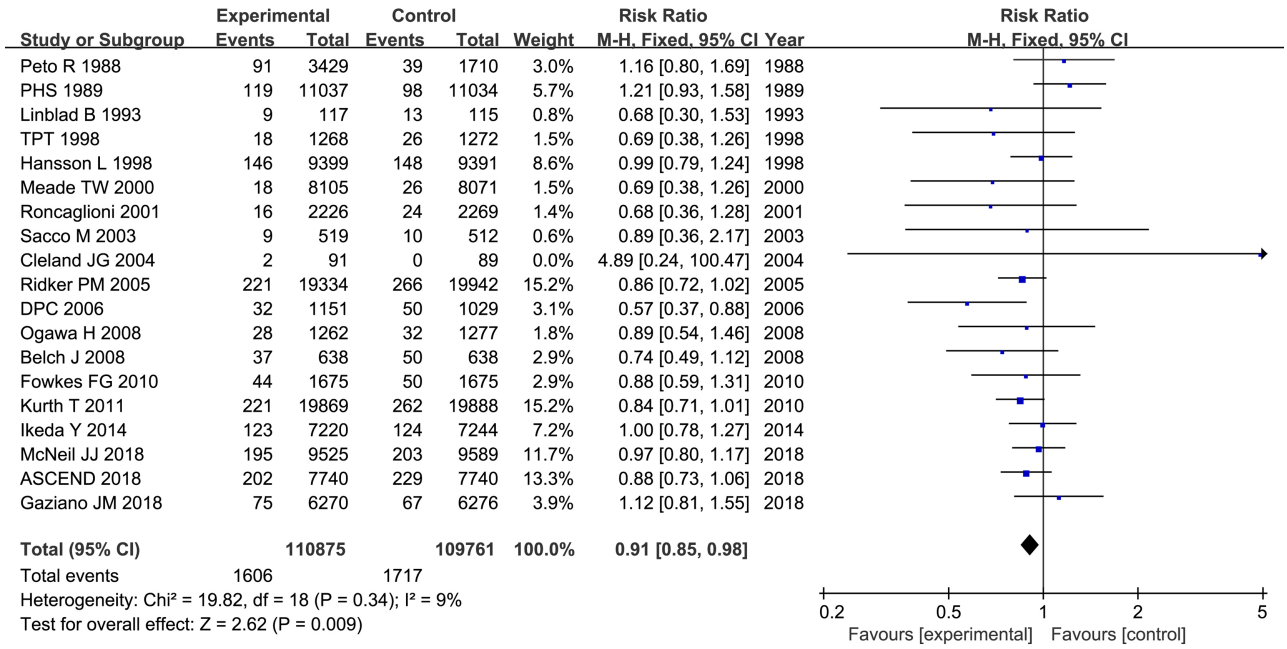

Figure 3. The effect of aspirin on the incidence of stroke.

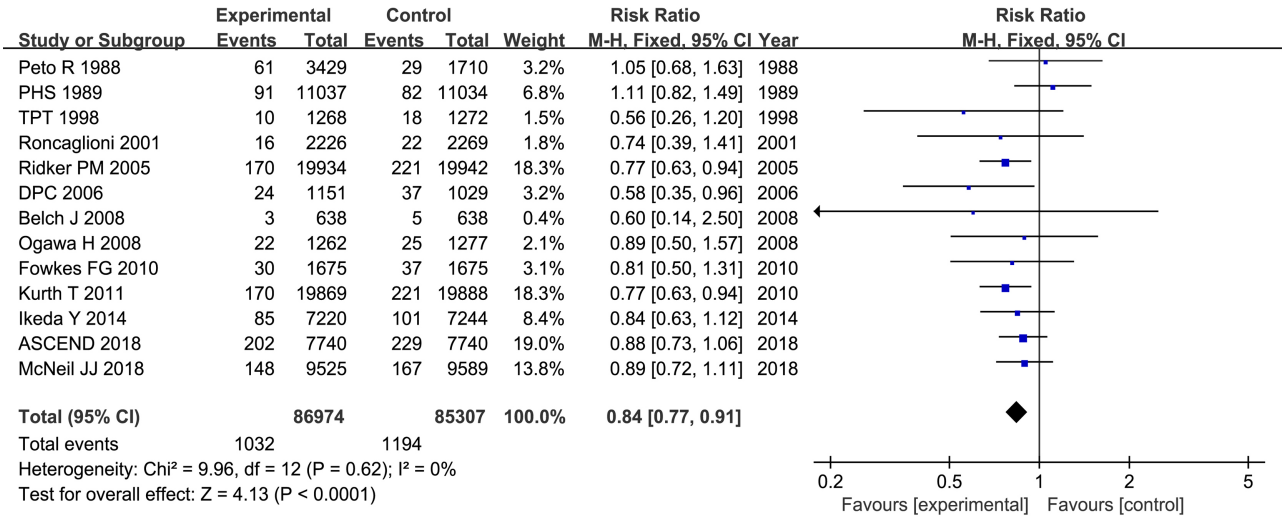

Figure 4. The effect of aspirin on the incidence of ischemic stroke.

3.3.3. Incidence of Hemorrhagic Stroke

15 studies [8] [9] [11] [12] [14] [17]-[26] reported the effect of long-term prophylactic aspirin use on the incidence of hemorrhagic stroke. The results showed that there was no heterogeneity among the studies (I^2 = 0%, P = 0.73), and a fixed-effect model [RR = 1.23, 95% CI (1.04, 1.46), P = 0.01] was used, indicating that it was comparable to the control group. Compared with the aspirin group, the incidence of hemorrhagic stroke was significantly increased, as shown in Figure 5.

3.3.4. Incidence of TIA

8 studies [10] [15] [17] [20] [21] [22] [23] [26] reported the effect of long-term prophylactic aspirin use on the incidence of TIA. The results showed that there was no heterogeneity among the studies (I^2 = 0%, P = 0.91). Using a fixed effect model, the incidence of TIA in the aspirin group was lower than that in the control group [RR = 0.80, 95% CI (0.72, 0.88), P < 0.0001], the difference was statistically significant, see Figure 6.

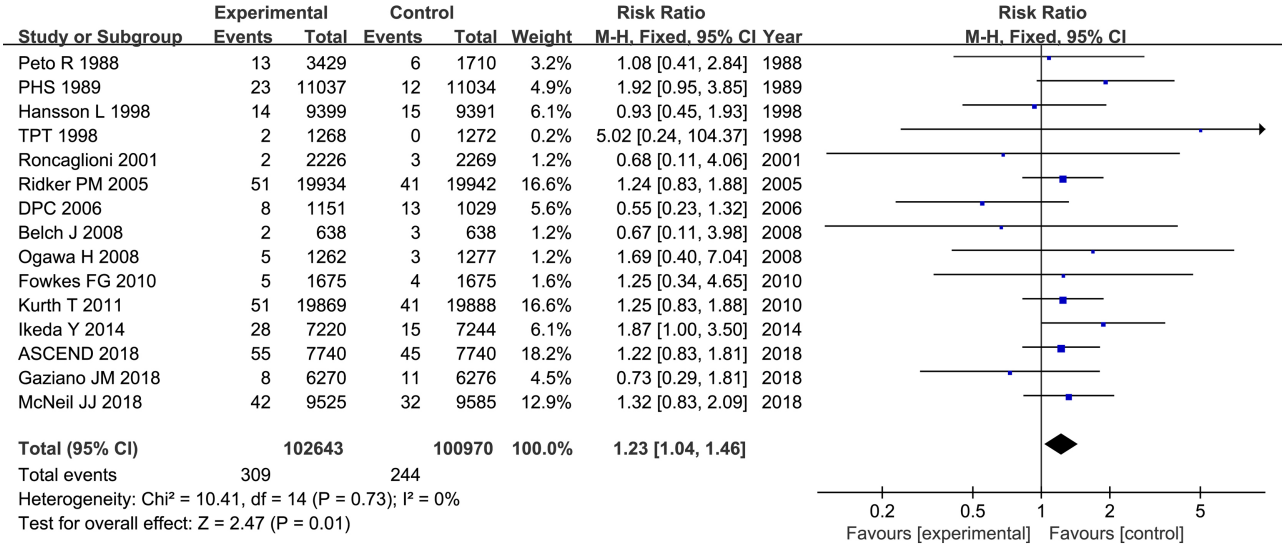

Figure 5. The effect of aspirin on the incidence of hemorrhagic stroke.

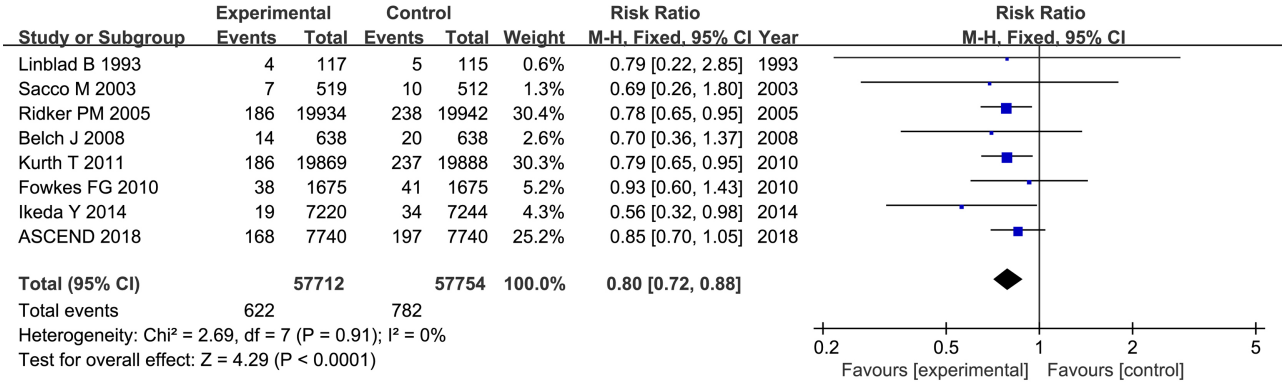

Figure 6. The effect of aspirin on the incidence of TIA.

3.3.5. Effects on Secondary Outcomes

17 studies [8] [9] [11] [12] [14]-[26] reported the effect of long-term prophylactic use of aspirin on the incidence of myocardial infarction. The results showed that there was heterogeneity among the results of each study ($P < 0.01$, $I^2 = 63\%$). According to different aspirin doses, they were divided into 2 subgroups, 75 mg and 100 mg. The results of subgroup analysis showed that different aspirin doses were the source of heterogeneity between studies. 12 studies [9] [11] [12] [14] [17] [19] [20] [21] [23] [24] [25] [26] reported an effect on the incidence of gastrointestinal bleeding. The results showed that there was heterogeneity among the results of each study ($P < 0.01$, $I^2 = 79\%$). The subgroup analysis of the heterogeneity showed that there was still a large heterogeneity, and only the descriptive analysis of the study results was carried out.6 studies [8] [9] [11] [13] [18] [24] described the dosage form of aspirin in detail, and one study [10] described the time of taking aspirin, suggesting that aspirin dosage form, time of taking may be a source of heterogeneity. 17 studies [8] [9] [10] [11] [12] [14] [16]-[26] reported the effect of long-term prophylactic aspirin use on mortality. The results showed that there was no heterogeneity among the results of the studies ($P = 0.66$, $I^2 = 0\%$). The fixed-effect model was used for Meta-analysis, and there was no significant difference in the mortality between the long-term preventive aspirin group and the control group. [$RR = 0.97$, 95% CI (0.93, 1.02), $P = 0.20$], the summary results are shown in **Table 2**.

3.3.6. Sensitivity Analysis

The included studies were excluded one by one, and the remaining studies were re-analyzed. The results showed that the combined effect size of the studies did not change significantly. Among the 19 studies included in the index of stroke incidence, one [22] study had the largest sample size (sample size was 39,757 cases). $RR = 0.93$, 95% CI (0.86, 1.00), $P < 0.05$], the results did not change significantly, suggesting that the results of this study are robust.

3.3.7. Publication Bias Assessment

A funnel plot was made for the 19 studies included in the stroke incidence indicator. The effect points of each study were centered on the combined effect size, roughly symmetrically distributed, and there was no publication bias, as shown in **Figure 7**.

Table 2. Meta-analysis results of secondary outcome indicators.

Secondary outcome measure	Number of included studies	Effect of pattern	Results of meta-analysis			I^2	P
			RR	95% CI	*P*		
Incidence of myocardial infarction	17 [8] [9] [11] [12] [14]-[26]	Random	0.85	0.75 - 0.97	<0.01	63.0	<0.01
Incidence of gastrointestinal bleeding	12 [9] [11] [12] [14] [17] [19] [20] [21] [23] [24] [25] [26]	Random	1.62	1.35 - 1.93	<0.01	79.0	<0.01
Mortality rate	17 [8] [9] [10] [11] [12] [14] [16]-[26]	Fixed	0.97	0.93 - 1.02	0.20	0	0.66

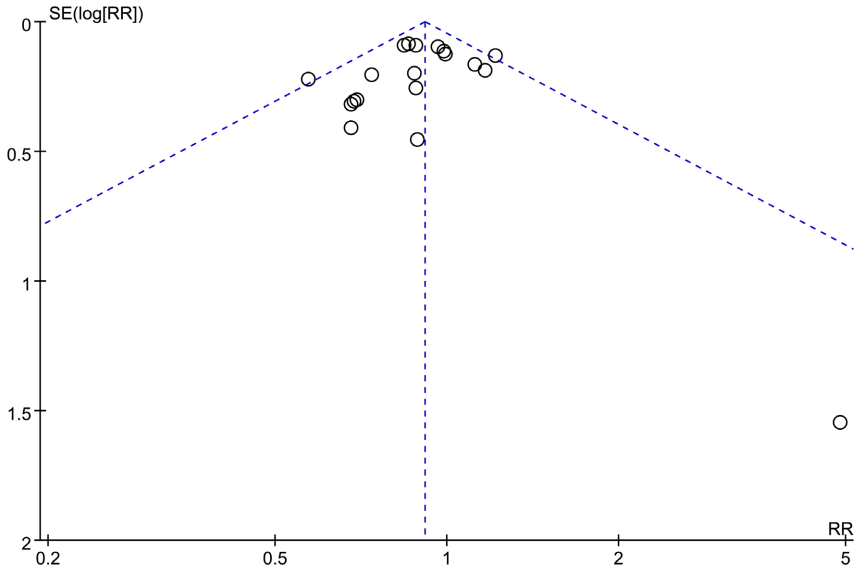

Figure 7. Publication bias detection results.

4. Discussion

4.1. Long-Term Prophylactic Use of Aspirin Reduces the Incidence of Stroke, Ischemic Stroke, and TIA

The results of this study showed that long-term preventive use of aspirin can effectively reduce the incidence of stroke, ischemic stroke and TIA. There may be two reasons for this result: 1) Aspirin is an anticoagulant widely used in clinical practice. Its mechanism of action is the irreversible binding of aspirin and cyclooxygenase-1 to inhibit the synthesis of thrombin A_2, thus blocking the platelet aggregation mediated by thrombin A_2, preventing and controlling thrombosis, and reducing the risk of ischemic cardiovascular and cerebrovascular diseases. Ischemic stroke accounts for about 68% - 80% of all strokes and is one of the common types of cerebrovascular diseases. Therefore, long-term prophylactic use of aspirin has become a major reason for the benefits of this group [27] [28] [29]. 2) Among the 19 included studies, except for Peto *et al.* [8] and Ridker *et al.* [17], who were healthy male doctors and healthy women respectively, most of the other included subjects were people with cardiovascular and cerebrovascular diseases or who were at high risk of cardiovascular and cerebrovascular diseases, so they could benefit from the preventive use of aspirin. In addition, Guirguis-Blak *et al.* [29] once again verified that people with high cardiovascular risk may benefit from prophylactic aspirin use. Further research is needed to determine whether healthy people at risk of cardiovascular disease can benefit from long-term prophylactic use of aspirin.

4.2. Long-Term Prophylactic Use of Aspirin Increases the Incidence of Hemorrhagic Stroke

Results of this meta-analysis showed that long-term prophylactic use of aspirin increased the incidence of hemorrhagic stroke compared with the control group.

Bleeding is a major risk and a major limitation of aspirin's widespread clinical use. In addition, age is not only a major risk factor for stroke, but also an important factor to be considered in the process of drug application. With the increase of age, the organ function and immune function of the body show a trend of gradual decline, so the tolerance of the elderly population to drugs is worse, more prone to adverse reactions. In this study, the average age of the included subjects > 50 years old, which may be an important reason for the increased incidence of hemorrhagic stroke. Therefore, in the latest guidelines, the applicable age of aspirin is reduced from the original 45 - 79 years old to 50 - 69 years old, in order to improve the safety of clinical medication [30].

4.3. Effects of Long-Term Prophylactic Use of Aspirin on Other Outcome Indicators

1) Aspirin can significantly reduce the incidence of myocardial infarction. Some domestic and foreign studies [31] [32] [33] have confirmed the safety and effectiveness of aspirin for primary cardiovascular prevention, and the results showed that aspirin can significantly reduce the incidence of myocardial infarction, which is consistent with the results of this study. 2) Increased incidence of gastrointestinal bleeding. Aspirin is a class of nonsteroidal drugs, and the main risk of long-term use is bleeding, the most common of which is gastrointestinal bleeding. In this study, 12 studies [9] [11] [12] [14] [17] [19] [20] [21] [23] [24] [25] [26] reported the impact on the incidence of gastrointestinal bleeding, and some studies [9] [11] [14] [17] [21] [23] [26] reported bleeding in other parts of the nose, retina, urinary system and so on. There is high heterogeneity among studies. On the one hand, due to different definitions of massive bleeding in the tests and differences in assessment tools, measurement results are inconsistent. On the other hand, the dose, dosage form and duration of aspirin were also a cause of heterogeneity. 3) No effect on mortality. The results of this study showed that long-term prophylactic aspirin use did not reduce the risk of death, which was different from the study of Li Wei *et al.* [4]. Since the follow-up years of the studies included in this meta-analysis ranged from 0.5 years to 10.1 years, the results may be affected to some extent, suggesting that researchers should continue to pay attention to the long-term effects of aspirin.

4.4. Limitation

This study only searched Chinese and English databases, and there may be incomplete literature inclusion. The research subjects included in the literature are quite different in terms of regions, races, cultural backgrounds, genetic factors, and economic levels, which may lead to heterogeneity among studies. Since the follow-up periods of the included studies vary (the shortest is 0.5 years, the longest is 10.1 years), the time span is long, the number of participants is large, and there are many confounding factors, which may have a certain impact on the results of the study. Only 1 domestic literature was included in this study [18], and the sample size was relatively small. Due to differences in regions, rac-

es, and physiques, the safety and efficacy of aspirin in the domestic population needs to be further verified.

4.5. Inspiration

This suggests that it is necessary for Chinese researchers to carry out high-quality, multi-center clinical randomized controlled trials and extend the follow-up time to further verify the safety and efficacy of long-term preventive use of aspirin in the population.

5. Conclusion

Long-term prophylactic use of aspirin can reduce the overall incidence of stroke, but there is also a risk of bleeding. The advantages and disadvantages of aspirin should be fully evaluated and strict screening should be carried out before medication, which can minimize adverse reactions and improve the safety and effectiveness of aspirin in the primary prevention of stroke.

Acknowledgements

This study was supported by nursing elite talent pool of Shanghai Pulmonary Hospital (HL-C3).

Conflicts of Interest

None of the authors has any potential conflicts of interest associated with this research.

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